American Journal of Medical Genetics 92:195–199 (2000)

Brief Clinical Report

Girl With Accelerated Growth, Hearing Loss, Inner Ear Anomalies, Delayed Myelination of the Brain, and del(22)(q13.1q13.2)

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We report on an 18-month-old Japanese girl with 46,XX,del(22)(q13.1q13.2). To our knowledge, this is the first report of a case of interstitial deletion of a 22q13.1–q13.2 segment. Clinical features included hearing loss accompanied by inner ear anomalies, hypotonia and minor anomalies, such as a long philtrum, full eyelids, epicanthus, left transverse palmar crease and psychomotor developmental delay. Despite the chromosomal deletion, her physical growth was accelerated: her height was between the 75th and 90th percentiles for her age. Her brain MRI showed signs of delayed myelination. The three-dimensional MRI of the inner ear showed abnormalities of the cochlea and vestibule in both ears. Clinical features of the patient are similar to those of a patient with a del(22)(q13.1q13.33) karyotype previously reported by Romain et al. [1990: J Med Genet 27:588–589]. Am. J. Med. Genet. 92: 195–199, 2000.

KEY WORDS: chromosome 22q deletion; accelerated growth; hearing loss; delayed myelination

INTRODUCTION

There have been many patients with deletion of 22q11 or 22q12 [Watt et al., 1985; Kirshenbaum et al., 1988; Driscoll et al., 1992; Fryburg et al., 1996; Bingham et al., 1997], most of which is associated with DiGeorge syndrome or velo-cardio-facial syndrome. To our knowledge, however, deletion of 22q13 band has been reported in only 18 patients [Herman et al., 1988; Romain et al., 1990; Zwaigenbaum et al., 1990; Narahara et al., 1992; Phelan et al., 1992; Nesslinger et al., 1994; Dohney et al., 1997; Wong et al., 1997; Schröder et al., 1998]. All of them were a terminal deletion involving 22q13, but only one had interstitial deletion of this segment [Romain et al., 1990]. Here we report on a girl with an interstitial deletion of a 22q13 segment and compare her clinical manifestations with those of previously reported patients.

CLINICAL REPORT

The patient, an 18-month-old girl, was the first child of healthy unrelated parents of Japanese ancestry. The father was 28 years old and the mother was 26 years old at the time of the patient's birth. There was no history of abortion, and the pregnancy was uneventful. The patient was born at 38 weeks of gestation by cesarean section for pelvic presentation. Birth weight was 3,620 g (90th percentile), length 50.5 cm (75th percentile) and OFC 37.5 cm (95th percentile). The Apgar score was 10 at one min.

At age 6 months, she was referred to our hospital because of poor response to sound. She was hypotonic, and had minor anomalies, including long philtrum, epicanthus, full cheeks, full eyebrows, full eyelids with ptosis (Fig. 1A), prominent auricles, high arched palate and left transverse palmar crease. At 8 months, she could roll over sometimes, but her head was unstable. Her subsequent clinical course was marked by profound psychomotor retardation. At 13 months, her developmental quotient was estimated at 46, being comparable to 6 months. She could not sit down or walk alone at age 18 months. In contrast, the patient's

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Received 17 June 1999; Accepted 16 February 2000

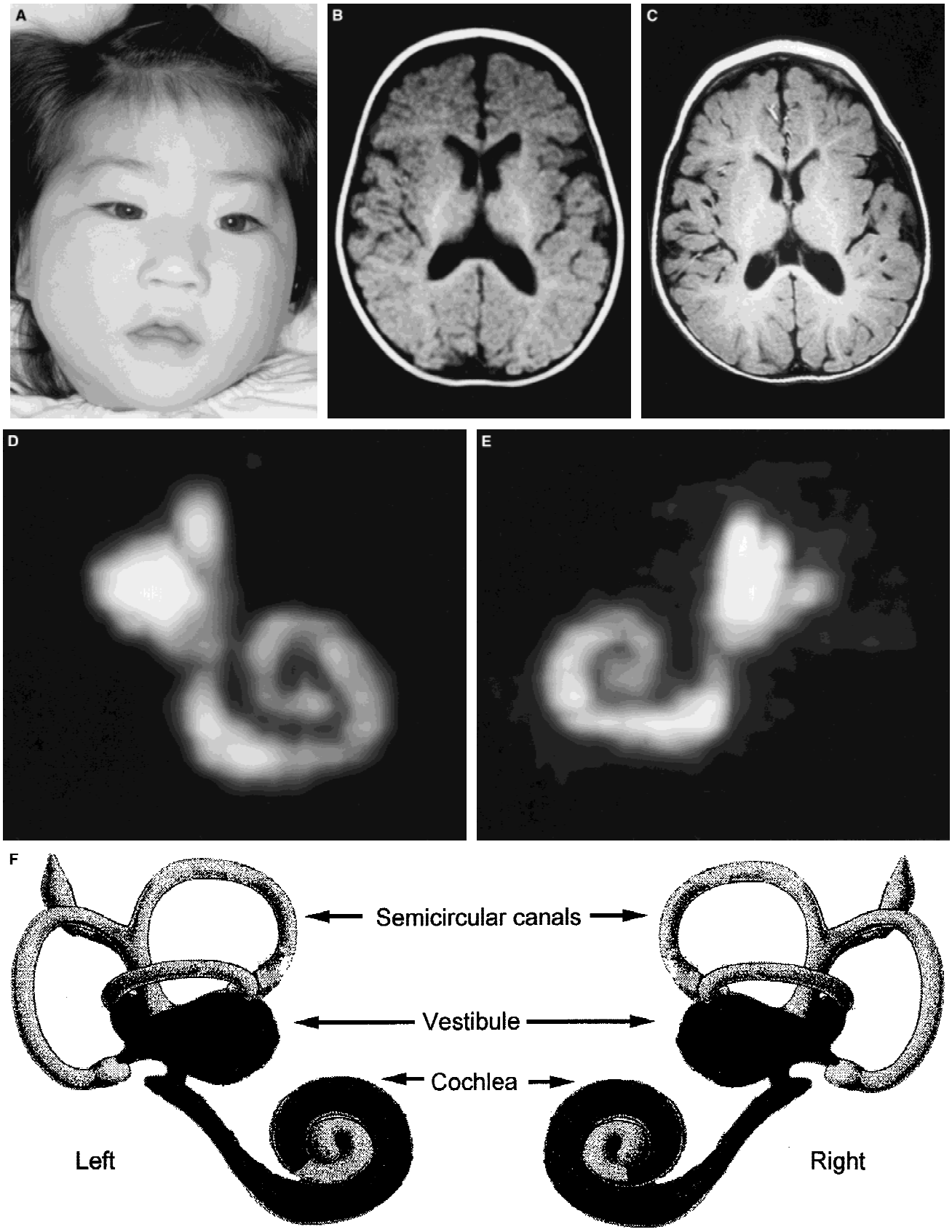

Fig. 1. Facial appearance at age 12 months (**A**), brain MRI (T2-weighted) at age 7 months (**B**) and at age 13 months (**C**), 3D-MRI of the inner ear (left, **D**; right, **E**), and its schema (**F**). Brain MRI shows high signal intensity only in the posterior limbs of the internal capsule (B), and U fibers are not present in any white matter (C). In the 3D-MRI, the cochlea has only one and a half turns in both ears, and there is a bubbled vestibule instead of three semicircular canals in each ear. The black part shows the remaining part (F).

growth has been above the average (Fig. 2). Physical examination at age 15 months showed that her body weight was 10,490 g (75th percentile) and her height was 82.1 cm (90th percentile) (Fig. 2).

Laboratory studies including serum amino acid levels, thyroid function, urine analysis, titers of TORCH, complete blood counts and a biochemistry screen test were all normal except for iron deficiency anemia, that was treated and resolved when she was 17 months old. Serum levels of growth hormone (GH) and somatomedin-C at 17 months were 3.13 ng/ml (normal range, 0.66–3.68 ng/ml) and 65.63 ng/ml (17–173 ng/ml), respectively, whereas serum somatostatin level was high at 65 pg/ml (normal range, 39.5–23.7 pg/ml). The activity of arylsulfatase A in her peripheral blood lymphocytes was 142.2 ng/min/mg prot (normal range, 60.5–144.0 ng/min/mg prot) [Baum et al., 1959]. Her bone age at 17 months was comparable to 18 months. Brain MRI at both 7 months and 13 months demonstrated delayed myelination (Fig. 1B,C). Her hearing tested by auditory brain stem response showed bilateral profound hearing loss. In either ear, she had no response to Caloric stimulation provided by 4-ml ice water. The three-dimensional MRI of the inner ear showed an abnormality of the cochlea and vestibule in both ears (Fig. 1D,E). The cochlea had only one and a half turns in both ears, and we found a bubbled vestibule instead of the three semicircular canals in each ear. Her profound hearing loss and lack of response to Caloric stimulation presumably resulted from these inner ear abnormalities. No abnormality in the urinary tract was detected by ultrasonography.

High-resolution GTG chromosome analysis revealed that the patient has a 46,XX,del(22)(q13.1q13.2) karyotype (Fig. 3A). The karyotypes of the parents were normal. Fluorescence in situ hybridization (FISH) was performed on the patient's metaphase chromosomes by using 22q cosmid clones (Health Science Research Resources Bank, Osaka, Japan) as probes to detect precise extent of the deletion. FISH with a cosmid clone (cHKA-19) assigned to 22q13.2–qter [Kurahashi et al., 1994] gave FITC signals on both homologous chromosomes 22 (Fig. 3B), indicating that this locus is outside the deletion extent. On the other hand, when using a cosmid clone (cHKAD-44) assigned to 22q12.1–q13.1, the signals appeared on only one of the homologues 22 (Fig. 3C), implicating that a region recognized with the probe was deleted. Thus, the interstitial deletion was confirmed as 46,XX.ish del(22)(q13.1q13.2)-(cHKA-19+,cHKAD-44–).

DISCUSSION

The patient described here has a del(22)(q13.1q13.2) karyotype. The result of FISH analysis and normal activity of arylsulfatase A in the lymphocytes, the gene of which is mapped to chromosome 22q13.3 [Geurts van Kessel et al., 1980; Narahara et al., 1992] indicate that a 22q13.3 segment is not deleted in her chromosome. Among the 18 previously reported patients with 22q13

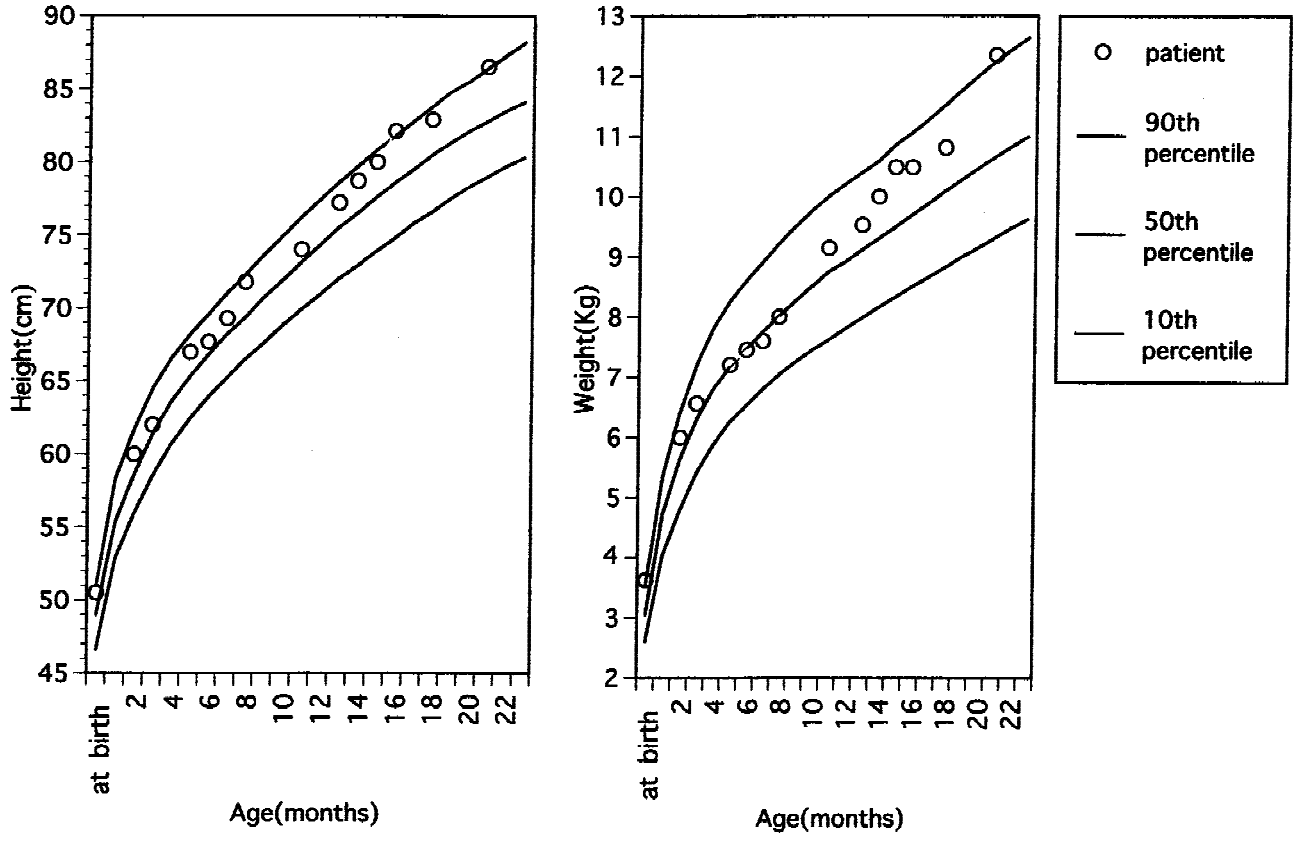

Fig. 2. Growth curve of our patient on the 1990 background standard curves for the Japanese children.

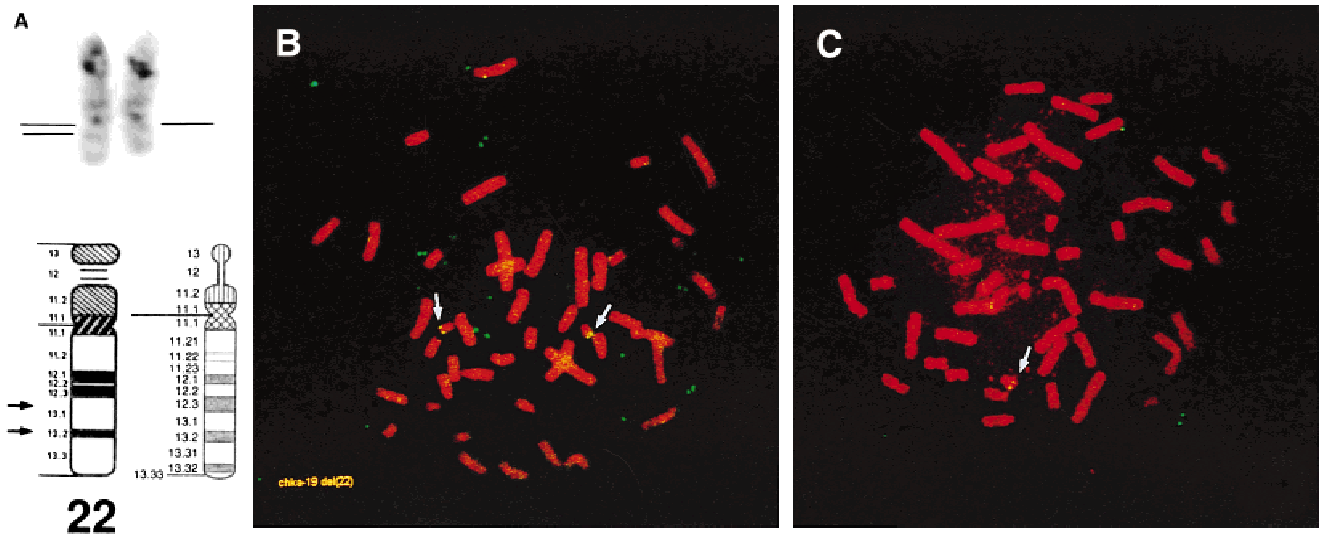

Fig. 3. GTG-banded chromosomes 22 (**A**) and FISH (**B** and **C**). Short-line and arrow indicate deleted segment and breakpoints, respectively. The cHKA-19 signals are seen on both chromosomes 22 (B), whereas the cHKAD-44 signals are on only one of #22 (C).

deletion [Herman et al., 1988; Romain et al., 1990; Zwaigenbaum et al., 1990; Narahara et al., 1992; Phelan et al., 1992; Nesslinger et al., 1994; Dohney et al., 1997; Wong et al., 1997; Schröder et al., 1998], there has been only one patient who had an interstitial deletion of a 22q13 segment [Romain et al., 1990] and no case of interstitial deletion involving a 22q13.1–q13.2 segment, as seen in our patient.

We compared the clinical manifestations of our patient with these 18 patients, especially with the patient by Romain et al. [1990], because the deletion extent was similar between our patient and the case of Romain et al. [1990]. We excluded the case reported by Wong et al. [1997] from the comparison, because the deletion of the case involved an extremely terminal segment. The manifestations common to the 17 patients included hypotonia, psychomotor developmental delay, accelerated growth, ptosis of eye lids, epicanthal folds, long philtrum, high arched palate and dysplastic ears or hearing loss (Table I). Dolichocephaly and high arched palate were evident in both ours and in several patients with del(22)(q13.3) (Table I). Both of our patient and patient by Romain et al. [1990] looked similar and had long philtrum, full eyebrows, full eyelids with ptosis, large ears, and transverse palmar creases. Dolichocephaly and high arched palate were evident in both ours and in several patients with del(22)(q13.3), but were not mentioned in the patient by Romain et al.

TABLE I. Clinical Features in Patients With 22q13 Detetion

	Present case 1998	Romain et al. [1990]	Schröder et al. [1998] (3 cases)	Dohney et al. [1997] (2 cases)	Nesslinger et al. [1994] (7 cases)	Narahara et al. [1992]	Zwaigenbaum et al. [1990] (2 cases)	Herman et al. [1998]
Deleted segment	q13.1–q13.2	q13.1–q13.33	q13	q13.32	q13.3	q13.31	q13.3	q13.31
Appropriate for gestational age	+	+	1/3	2/2	7/7	+	?	+
Normal or accelerated growth	+	+	2/3	1/2	2/7	–	2/2	+
Hypotonia	+	+	3/3	2/2	7/7	+	2/2	?
Developmental delay	+	+	3/3	2/2	7/7	+	2/2	+
Hearing loss	+	±	3/3	?	?	?	?	+
Speech delay	+	+	3/3	2/2	7/7	+	2/2	+
Delay in myelination	+	?	?	1/2	?	?	?	?
Brain atrophy	+	?	1/3	1/2	4/7	–	?	+
Minor anomalies								
Dolicocephaly	+	–	1/3	0/2	6/7	–	?	+
Ptosis of eyelid	+	+	?	0/2	3/7	?	?	+
Epicanthus	+	+	?	1/2	4/7	–	?	+
Long philtrum	+	+	?	?	?	?	2/2	?
Dysplastic ears	+	+	?	0/2	6/7	+	2/2	+
High arched palate	+	–	1/3	?	1/7	+	?	+
Simian crease	+ (L)	+	1/3 (L)	?	1/7 (L)	?	?	+ (L)
Syndactyly	–	–	?	?	1/7	+	?	–
Kidney abnormality	–	?	2/3	?	?	?	?	+
Heart defect	–	?	2/3	1/2	?	?	?	–

[1990]. The hearing loss in our patient was accompanied by inner ear anomalies that were confirmed by the 3D-MRI, but that in the patient of Romain et al. [1990] has mild conductive hearing loss with exudative otitis (personal communication). Inner ear anomalies are relatively common in children with sensorineural hearing loss [Jackler et al., 1987], but the association of the anomalies with chromosomal abnormality is uncommon [Newton, 1985]. Because the deletion in our patient is confined to 22q13.1–q13.2, her inner ear anomalies are less likely related to the acoustic neurofibromatosis gene (*NF2*) that is localized to 22q12.2 [Arai et al., 1992; Trofatter et al., 1993]. Brain MRI demonstrated delayed myelination in our patient. Brain atrophy was reported in 7 cases of 22q13 deletion [Herman et al., 1988; Nesslinger et al., 1994; Dohney et al., 1997; Schröder et al., 1998].

Normal or accelerated growth is characteristic in patients with deletion 22q13. The growth curve of our patient was somewhat higher than the average. Her serum somatostatin level was found to be high, but serum levels of GH and somatomedin-C were within the normal range. Somatostatin is known to inhibit GH secretion by binding to the somatostatin receptor. The gene for the somatostatin receptor family is localized on 22q13.1 or 13.3 [Yamada et al., 1993; Kolakowski et al., 1996]. If somatostatin receptor activity is decreased, secretion of GH and somatomedin-C may increase, resulting in accelerated growth. Further studies are necessary to clarify whether the somatostatin receptor function is deficient in our patient.

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